Enhancers of innate and adaptive immunity combine with membrane bound IL15 to increase the efficacy of tumor infiltrating lymphocyte (TIL) therapy for tumors with immunosuppressive microenvironments

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Background

The clinical impact of tumor infiltrating lymphocytes (TIL) cell products is currently limited by suboptimal persistence and potency, as well as the need for high-dose adjuvant IL-2 treatment, which is associated with severe toxicities. Thus, we engineered an IL-2-independent TIL product, based on regulated expression of interleukin 15 (cytoTILs™) cells, which has shown anti-tumor efficacy and persistence in human melanoma PDX models. Since the immuno-suppressive tumor microenvironment (TME) hinders cell therapies, we hypothesized that combining pleotropic cytokines of the interferon (IFN), IL-1, or TNF families with IL-15 would further enhance antitumor activity and that our cytoDRiVE® platform would allow pharmacologic control of these potent immune mediators. We tested constitutive and regulated combinations of a representative member of these cytokines with IL-15 in human TIL for in vitro polyfunctionality and in vivo antigen-independent persistence. We also engineered mouse pml-TCR cells with cytokine combinations for evaluation in the syngeneic B16 melanoma model.

Results

Expression of enhancers of innate and adaptive immunity is efficiently regulated in Jurkat cells and engineered Tumor-Infiltrating Lymphocytes (TILs)

- IL18: constitutive expression of IL18 on Jurkat cells and TILs
- TNFSF-X: regulatable expression of TNFSF-X on Jurkat cells and TILs

TILs transduced with constitutive mbIL15 and regulated IFNα expand with increased polyfunctionality

- Mice engrafted with CD8 pml-TCR-transgenic T cells expressing IL18 and IL15 show improved control of B16 tumors and a pro-inflammatory tumor microenvironment

Conclusions

- Obsidian’s cytoDRiVE® platform allows pharmacologic control of potent immune mediators including IL18, IFNα and TNFSF-X
- cytoTILs™ cells, Obsidian’s TIL expressing mbl15 that expand and persist without IL-2, can be further engineered to express regulated enhancers of innate and adaptive immunity that can modify the tumor microenvironment to enhance TIL potency for solid tumors marked by an immunosuppressive TME